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Obesity-induced increase of CYP2E1 activity and its effect on disposition kinetics of chlorzoxazone in Zucker rats

Phisit Khemawoot, Koichi Yokogawa, Tsutomu Shimada, Ken-ichi Miyamoto

Department of Medicinal Informatics, Division of Cardiovascular Medicine, Graduate School of Medical Science, Kanazawa University, Japan

Abstract

This study was designed to investigate the induction of CYP2E1 in obese Zucker rats and its effect on the disposition kinetics of chlorzoxazone (CZX). CZX 20 mg/kg was administered to three groups of rats: normal Zucker rats fed a normal diet (ND), normal Zucker rats fed a high-fat diet (HF), and genetically obese Zucker (fa/fa) rats fed a normal diet (OB). The values of the area under the plasma concentration-time curve from 0 to \( t \) (AUC\(_t\)) of CZX were in the order of ND > HF > OB rats. The AUC\(_t\) values of total 6-hydroxychlorzoxazone (6OHCZX-T), which is considered to be a CYP2E1 metabolic marker, were in the opposite order. The values of the AUC\(_t\) ratio (6OHCZX-T/CZX) in ND, HF and OB rats were approximately 0.2, 0.3 and 0.4, respectively. The CZX concentration in fat was much higher than the concentrations in plasma, liver and kidney in all groups. Induction of CYP2E1 protein was greater in both liver and fat of OB rats than in those of HF rats. Microsomal activity of CYP2E1 in liver and fat was also in the order of OB > HF > NM rats. These results suggest that CYP2E1 may be induced in liver and fat of obese patients, thereby potentially altering the disposition kinetics of not only CZX, but also other lipophilic drugs metabolized by CYP2E1.

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[3,4]. The overfed normal rat can also mimic physiological aspects of severe obesity in humans, such as hypercholesterolemia, hyperinsulinemia, etc. [5,6].

Changes in physiological status, such as obesity and hypercholesterolemia, can modulate the metabolic activity of CYP2E1 [7–9]. Interestingly, CYP2E1 is a ubiquitous enzyme that is distributed in various organs of animals, but obesity-related increase of CYP2E1 activity is well documented only in liver.

There are several reports that the hydroxylation of chlorzoxazone (CZX) can be used as an indicator of CYP2E1 activity both in vivo and in vitro [10,11]. CZX is a muscle relaxant that is distributed in various organs of animals, but obesity-related increase of CYP2E1 activity is well documented only in liver. There are several reports that the hydroxylation of chlorzoxazone (CZX) can be used as an indicator of CYP2E1 activity both in vivo and in vitro [10,11]. CZX is a muscle relaxant that is distributed in various organs of animals, but obesity-related increase of CYP2E1 activity is well documented only in liver.

2. Materials and methods

2.1. Materials

CZX and 6OHCZX were purchased from Sigma–Aldrich Inc. (St. Louis, MO). High-fat diet (LABO H Standard) and normal diet (LABO MR Stock) were purchased from Nusan Corp. (Yokohama, Japan). The high-fat diet contained 6.5% (w/w) fat (total energy 259.2 kcal/100 g), while the normal diet (Yokohama, Japan). The high-fat diet contained 6.5% (w/w) fat (total energy 346.7 kcal/100 g), while the normal diet contained 4.1% (w/w) fat (total energy 259.2 kcal/100 g).

2.2. Animal treatment

Male 8-week-old Zucker (+/+) rats and genetically obese Zucker (fa/fa) rats were purchased from Japan SLC Inc. (Toyama, Japan). The rats were divided into three groups: normal Zucker (+/+) rats fed with normal diet (ND rats), normal Zucker (+/+) rats fed with high-fat diet (HF rats) and genetically obese Zucker (fa/fa) rats fed with normal diet (ND rats). The animals were housed for 3 months in a climate- and light-controlled environment with free access to water and the designated food. All animal procedures were in accordance with the standards set forth in the guidelines for the care and use of laboratory animals at the Takara-machi Campus of Kanazawa University.

2.3. Disposition kinetic of CZX

CZX (20 mg) was dissolved in 400 μl of 0.5N NaOH and diluted with 600 μl of normal saline solution (20 mg/ml). This solution was administered to rats at a dose of 20 mg/kg by i.v. administration over 2 min via a lateral tail vein. Then, approximately 0.2–0.5 ml of blood was collected from the tail vein on the other side at 0.03, 0.08, 0.25, 0.5, 1, 2, 4, and 8 h after completion of the administration of CZX. The blood was centrifuged at 3000 × g for 10 min, and the plasma was collected. Some rats were killed by decapitation at 4 h after CZX administration, and the liver, kidney and abdominal fat were quickly excised, rinsed well with ice-cold saline, blotted dry, and weighed. Each tissue sample was homogenized with normal saline and stored at −80 °C until analysis.

2.4. Sample preparation

The concentrations of CZX and 6OHCZX in biological samples were analyzed as unchanged and glucuronidated fractions. The assay of glucuronidated CZX and 6OHCZX was performed according to Frye and Stiff [15] with slight modifications. Briefly, a 100 μl sample of plasma or tissue homogenate was added to 300 μl of 0.2 M phosphate buffer (pH 6.5) containing 500 units of β-glucuronidase. The mixture was incubated at 37 °C with shaking for 2 h, and then the reaction was stopped by adding 100 μl of acetonitrile containing phenacetin (1 μg) as an internal standard for HPLC analysis.

2.5. HPLC assay of CZX and 6OHCZX

To a 100 μl of sample solution was added 5 ml of diethyl ether, then the mixture was shaken vigorously for 10 min, and centrifuged at 3000 × g for 10 min. The ether layer was transferred to another tube for evaporation in a vacuum centrifugal concentrator. In the case of adipose tissue, reverse phase extraction from the aqueous phase of homogenated samples was done by adding 0.5N NaOH to the samples and mixing. The aqueous phase was collected and titrated with an equal amount of 0.5N HCl. Next, diethyl ether (5 ml) was added to extract CZX and 6OHCZX from aqueous phase, and the organic solution was further processed as described above.

The residue from evaporation was dissolved in 200 μl of the mobile phase, and a 50 μl aliquot was injected into an HPLC system (LC-9A, Shimadzu Co. Ltd., Kyoto, Japan) equipped with a CAPCELL PAK C18 column, 1.5 mm i.d. × 150 mm (Shiseido Co. Ltd., Tokyo, Japan). The mobile phase consisted of 25% (v/v) acetonitrile in 50 mM KH₂PO₄ (pH 4.0), pumped at a rate of 0.1 ml/min. The absorbance was detected at wavelengths of 295 and 287 nm for 6OHCZX and CZX, respectively [14,16]. The retention times of 6OHCZX, phenacetin and CZX were approximately 5, 12 and 20 min, respectively. Linear calibration curves (r > 0.999) were obtained for both compounds in plasma over the concentration range from 1 to 150 μg/ml. The limits of detection were estimated to be 0.25 μg/ml for both CZX and 6OHCZX.

2.6. Reverse transcriptase polymerase chain reaction (RT-PCR) assay

Total RNA was isolated from liver, kidney and fat with Isogen (Nippon Gene Co. Ltd., Toyama, Japan). Each RNA sample (1 μg) was reversed-transcribed at 37 °C for 2 h, and the cDNA was amplified with a Peltier Thermal Cycler PTC-100 (Bio-Rad Laboratories Inc., Hercules, CA). The numbers of amplification cycles were 30 for fat cDNA and 25 for cDNAs from other tissues. PCR products were evaluated by electrophoresis on 2% (w/v) agarose gel stained with ethidium bromide, and photographed under UV trans-illumination. The product size was estimated by comparison with a 100 bp DNA ladder.
2.9. Measurement of hydroxylation activity of microsomal CYP2E1

The enzyme activity of microsomal CYP2E1 was determined by the measurement of 6OHCZX formation according to Chittur and Tracy [19], with minor modifications. A mixture of the microsomal solution (equivalent to 4 mg protein) and 50 mM phosphate buffer (pH 7.4) containing 50 μM CZX and 1 mM NADPH (final, 200 μM) was incubated at 37 °C for appropriate times. The reaction was stopped by adding 100 μL of acetonitrile containing phenacetin (1 μg) as an internal standard for HPLC assay. The 6OHCZX formed was extracted with diethyl ether and measured by HPLC as described above.

Table 1 – Physical and biochemical data in rats with obesity

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ND</th>
<th>HF</th>
<th>OB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>385 ± 5.0</td>
<td>410 ± 17.3</td>
<td>480 ± 8.3</td>
</tr>
<tr>
<td>Liver (g)</td>
<td>5.94 ± 0.42</td>
<td>6.22 ± 0.64</td>
<td>11.85 ± 0.88</td>
</tr>
<tr>
<td>Kidney (g)</td>
<td>2.11 ± 0.08</td>
<td>2.13 ± 0.14</td>
<td>2.23 ± 0.12</td>
</tr>
<tr>
<td>Epididymal fat (g)</td>
<td>3.49 ± 0.64</td>
<td>4.35 ± 1.12</td>
<td>12.74 ± 1.63</td>
</tr>
<tr>
<td><strong>Biochemical data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.26 ± 0.23</td>
<td>4.30 ± 0.10</td>
<td>4.07 ± 0.06</td>
</tr>
<tr>
<td>T-bilirubin (mg/dl)</td>
<td>0.057 ± 0.006</td>
<td>0.057 ± 0.012</td>
<td>0.28 ± 0.03</td>
</tr>
<tr>
<td>T-cholesterol (mg/dl)</td>
<td>75 ± 1.5</td>
<td>81 ± 2.1</td>
<td>88 ± 1.5</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.29 ± 0.02</td>
<td>0.30 ± 0.02</td>
<td>0.31 ± 0.01</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>81 ± 7.0</td>
<td>79 ± 3.1</td>
<td>83 ± 6.6</td>
</tr>
<tr>
<td>Cholinesterase (IU/l)</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
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</table>

Data were presented as mean ± S.D. of four rats. *Significant difference from ND rats at P < 0.05. **Significant difference from ND rats at P < 0.01.

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2.11. Data analysis

The pharmacokinetic parameters were calculated according to
model-independent moment analysis as described by Yamaoka
et al. [21]. Electrophoregrams after RT-PCR and immunopositive
bands were evaluated in arbitrary units by using NIH Image
software. Comparisons of numerical data among groups were
made by one-way ANOVA, with P < 0.05 as the criterion of a
significant difference. For each significant effect, a multiple
comparison test was performed with Scheffe’s test to verify the
difference between groups at P-values of 0.05 and 0.01, using
SPSS 10.0 from SPSS Inc. (Chicago, IL).

3. Results

3.1. Physical and biochemical data

Table 1 summarizes the physical data for ND, HF and OB rats.
The body, liver and epididymal fat weights of OB rats were
significantly higher than those of ND rats. The fat tissue
weight of HF rats, although slightly higher, was not significa-
tively different from that of ND rats. The value of total
bilirubin of OB rats was significantly higher than that of ND
rats, but liver function (AST) and kidney function (creatinine)
were unaffected. Total cholesterol was significantly increased
in HF rats and OB rats compared with normal rats.

Table 2 shows the pharmacokinetic parameters of
CZX and 6OHCZX-T after administration of CZX 20 mg/kg in
ND rats. Table 2 shows the pharmacokinetic parameters of
CZX and 6OHCZX-T after administration of CZX 20 mg/kg in
ND rats. The pharmacokinetic parameters in HF rats were interme-
tiate between those in OB rats and ND rats. Moreover, the AUC0
values of 6OHCZX-T in HF and OB rats were significantly higher than
that of ND rats.

Table 2 – Pharmacokinetic parameters of CZX and 6OHCZX after an i.v. administration of CZX 20 mg/kg over 2 min

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Rats</th>
<th>ND</th>
<th>HF</th>
<th>OB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CZX</td>
<td>AUC0 (μg·h/ml)</td>
<td>204 ± 14</td>
<td>181 ± 12</td>
<td>155 ± 21</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>1.67 ± 0.18</td>
<td>1.38 ± 0.19</td>
<td>1.19 ± 0.23</td>
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<tr>
<td>MRT (h)</td>
<td>2.40 ± 0.19</td>
<td>2.30 ± 0.28</td>
<td>2.00 ± 0.17</td>
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<tr>
<td>Cltot (l/h·kg)</td>
<td>0.014 ± 0.002</td>
<td>0.122 ± 0.010</td>
<td>0.145 ± 0.013</td>
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</tr>
<tr>
<td>Vdss (l/kg)</td>
<td>0.239 ± 0.014</td>
<td>0.277 ± 0.014</td>
<td>0.285 ± 0.016</td>
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<tr>
<td>6OHCZX-T</td>
<td>AUC0 (μg·h/ml)</td>
<td>41.2 ± 4.7</td>
<td>60.3 ± 4.2</td>
<td>71.6 ± 5.9</td>
</tr>
</tbody>
</table>

Data were presented as mean ± S.D. of four rats. Significant difference from ND rats at P < 0.05. **Significant difference from ND rats at P < 0.01.

* AUC from 0 to ∞.
* Half life.
* Mean residence time.
* Total clearance.
* Volume of distribution at steady state.

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Fig. 2 – Tissue and plasma concentrations of CZX and its glucuronide (CZX-G) at 4 h after an i.v. administration of CZX (20 mg/kg) over 2 min in ND (○), HF (□) and OB (▲) rats. Each column and bar represents the mean ± S.D. of four rats. *Significant difference from ND rats at P < 0.05. **Significant difference from ND rats at P < 0.01.

Fig. 3 shows the tissue concentration of CZX compared with the plasma concentration at 4 h after the i.v. administration of CZX. The CZX concentration in fat tissue was considerably higher than those of plasma, kidney and liver. The concentration of CZX-G was higher in HF rats and OB rats than ND rats. Fig. 3 shows the tissue concentrations of 6OHHCZX and its glucuronide in fat, liver and kidney at 4 h after the i.v. administration of CZX. The concentrations of both 6OHHCZX and 6OHHCZX-G in plasma and all tissues tended to be higher in the HF rats and OB rats than those in the ND rats. Interestingly, the kidney concentration was much higher than those of other tissues, and the concentration of 6OHHCZX-G in kidney of OB rats was significantly higher than that of ND rats.

3.3. Expression of CYP isoform mRNAs and proteins

The mRNA expression of CYP2E1 in liver of HF rats and OB rats was only slightly higher than that in ND rats, whereas, the relative expression of CYP2E1/β-actin in fat tissue from HF rats and OB rats was apparently higher than that in ND rats (Fig. 4).

Fig. 4 – Effect of obesity on the expression of CYP2E1 mRNA compared with β-actin in liver, kidney and fat of ND (○), HF (□) and OB (▲) rats. Each column and bar represents the mean ± S.D. of four rats. *Significant difference from ND rats at P < 0.05. **Significant difference from ND rats at P < 0.01.

The expression levels of CYP2E1 protein in the liver, kidney and fat tissue were examined by immunoblot analysis. The protein levels of CYP2E1 in the liver and fat of HF rats and OB rats were conspicuously increased compared with those of ND rats. Furthermore, the relative expression of CYP2E1/β-actin in liver microsomes and fat microsomes of HF and OB rats was significantly higher than that in ND rats (Fig. 5).

3.4. In vitro CYP2E1 and UGTs activity

Fig. 6 shows the hydroxylation activity of microsomal CYP2E1 in terms of 6OHHCZX formation from CZX, in various tissues from the three groups of rats. The highest hydroxylation rate was found in the liver compared with kidney and fat tissue. The activities in liver and fat from HF rats and OB rats were significantly higher than those in ND rats, whereas, no difference was seen in the kidney.

Fig. 7 shows the glucuronidation activity of microsomal UGTs in liver and kidney towards PNP, CZX and 6OHHCZX. The glucuronidation rates in the kidney of HF rats and OB rats were generally significantly higher than those in ND rats. The glucuronidation activity in fat was negligible in all groups. Interestingly, the glucuronidation of CZX was very much lower than that of 6OHHCZX, although the enzyme activity in the liver was not affected by obesity.

4. Discussion

Zucker (fa/fa) rats at 20 weeks of age showed markedly increased body weight, accompanied with an enlarged liver and increased epididymal fat, compared with Zucker (+/+). In contrast, Zucker (+/−) rats fed with high-fat diet (twice the level in normal diet) for 12 weeks did not show any significant physical or biochemical changes (Table 1).

CZX is well known to be a specific probe for CYP2E1, being hydroxylated to 6OHHCZX [10,11], which in turn is rapidly glucuronidated to 6OHHCZX-G [13]. Therefore, the appropriate
indicator for determining CYP2E1 activity in vivo should be the total amount of 6OHCZX generated after the administration of CZX, as reported in Fig. 1 and Table 2. The limited sampling time course of 8 h post-administration was contributed to the detection limits of both CZX and 6OHCZX. Most of 6OHCZX in biological samples was lower than the detection limit, and some of CZX levels were under the linearity of calibration curves at 12 h after administration of CZX. The administration of CZX 20 mg/kg to OB rats afforded lower values of AUC<sub>0-6</sub> and T<sub>1/2</sub> in serum as compared with those in ND rats, while the values of CL<sub>tot</sub> and V<sub>dss</sub> were significantly higher (Table 2). Based on the V<sub>dss</sub> and the tissue concentration of CZX (Fig. 2), it appears that lipophilic substances, such as CZX, penetrate well into the fat reservoirs of OB rats. The fat to plasma ratio of CZX was two to four folds both at 1 and 4 h of tissue sampling time, and the OB rats showed the higher trend of accumulation (data not shown for 1 h). Therefore, if CYP2E1 were not induced in the fat of OB rats, it is likely that the elimination rate of CZX would be delayed. However, the T<sub>1/2</sub> of CZX in OB rats was shorter than in ND rats, and further, the value of 6OHCZX in fat higher than the plasma level (Fig. 3). It is unlikely that 6OHCZX from blood would accumulate in fat, because 6OHCZX is relatively hydrophilic and is rapidly glucuronidated by UGTs located in smooth endoplasmic reticulum, the same location as that of CYP2E1 [22]. Therefore, the induction of CYP2E1 in fat, in addition to liver, may play a pivotal role in determining the disposition kinetics of CZX in obese rats. We also found that the AUC<sub>0-6</sub> ratio of 6OHCZX–T/CZX in HF rats and OB rats was 1.5–2 times higher than that in ND rats, reflecting the increased total activity of CYP2E1 in rats with obesity. Lucas et al. [7] reported that the 6OHCZX–T/CZX ratio (0.4) in obese or hyperlipidemic patients was higher than that (0.3) in normal subjects, in agreement with our finding. These results suggest that obesity and feeding of a high-fat diet can induce CYP2E1 activity in both humans and rats.

We found that both the protein content and activity of CYP2E1 were increased in microsomes of the liver from HF rats and OB rats, while there was no change in the kidney. Kobayashi et al. [23] reported that CZX was extensively metabolized in rat microsomes not only by CYP2E1, but also by CYP1A2 and CYP3A. Therefore, we also examined the mRNA expression and protein content of CYP1A2 and CYP3A, but found that they were unaffected by obese status (data not shown). Enriquez et al. and Irizar et al. [24,6] reported that CYP2E is poorly expressed in obese Zucker rats, which is consistent with our finding. However, Enriquez et al. [24] reported that CZX hydroxylase activity and CYP2E1 protein content were lower in Zucker (fa/fa) rats than in lean (+/?) littermates. There are various differences between their experimental conditions and ours, but one of the most important factors could be the influence of aging in obese Zucker (fa/fa) rats. Young obese Zucker (fa/fa) rats do not exhibit pathological conditions such as physical obesity, insulin resistance, etc., and usually have a lower CYP2E1 activity than their lean littermates, whereas, after the appearance of pathological symptoms at approximately 14–16 weeks of age, expression of CYP2E1 is increased. Therefore, we used Zucker (fa/fa) rats at 20 weeks of age in our study, when their pathological condition appeared to resemble that of severe obesity in humans. The report by Enriquez et al. [24]...
did not mention the physical condition of either the lean or obese Zucker rats, so that it is difficult to compare their findings and ours. Interestingly, the CYP2E1 mRNA isomoph was expressed in fat tissue, and its expression level and activity were significantly higher in HF rats and OB rats than in ND rats (Figs. 4–6). Yoshinari et al. [25] and Wan et al. [26] reported that the expression levels of both CYP2E1 mRNA and protein were increased in adipose tissue of fasting rats. However, the amount of adipose tissue in fasting rats was small, and so CYP2E1 in fasting animals may contribute little to the pharmacokinetics of its substrates compared with the situation in obese animals.

The hydroxylated metabolite of CZX (6OH CZX) has been reported to be excreted in bile to only a small extent; rather it undergoes rapid glucuronidation with subsequent excretion of the conjugate in urine [13]. We found that the glucuronida- tion activity in kidney microsomes was significantly higher in HF rats and OB rats than ND rats (Fig. 7), and the concentration of 6OH CZX glucuronide in the kidney was higher than that in the liver (Fig. 3). Since there is no evidence that a specific UGT subfamily is involved in glucuronide conjugation of CZX and 6OH CZX, we used PNP, a general marker for glucuronidation, to confirm our results. The glucuronidation activity towards PNP in kidney microsomes of HF and OB rats showed the same trend as did the activity towards CZX and 6OH CZX. However, the glucuronidation activity in liver microsomes was not influenced by the high-fat diet or obese status, and was quite different towards different substrates. This suggests the presence of different UGTs isoforms in liver and kidney.

Further research will be required to identify the UGTs isoform(s) responsible for 6OH CZX glucuronidation in tissues, and the species that are affected by obese status.

In conclusion, CYP2E1 activity was induced in the liver fat tissues of obese animals, and glucuronidation activity was induced in the kidney. As a result, the disposition kinetics of CZX was markedly changed in obesity, with an increase in hydroxylation of CZX to form 6OH CZX, and an acceleration of 6OH CZX glucuronidation, resulting in rapid excretion in urine. Other drugs that are metabolized by CYP2E1 and UGTs may show similar changes of disposition kinetics in obese patients, resulting in reduced potency and shorter duration of action.

**References**


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